The Chemistry of Dimethyl Carbonate

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ABSTRACT

Dimethyl carbonate (DMC) is a versatile compound that represents an attractive eco-friendly alternative to both methyl halides (or dimethyl sulfate) and phosgene for methylation and carbonylation processes, respectively. In fact, the reactivity of DMC is tunable: at $T = 90$ °C, methoxycarbonylations take place, whereas at higher reaction temperatures, methylation reactions are observed with a variety of nucleophiles. In the particular case of substrates susceptible to multiple alkylations (e.g., CH_2-active compounds and primary amines), DMC allows unprecedented selectivity toward mono-C- and mono-N-methylation reactions. Nowadays produced by a clean process, DMC possesses properties of nontoxicity and biodegradability which makes it a true *green reagent* to use in syntheses that prevent pollution at the source. Moreover, DMC-mediated methylations are catalytic reactions that use safe solids (alkaline carbonates or zeolites), thereby avoiding the formation of undesirable inorganic salts as byproducts. The reactivity of other carbonates is reported as well: higher homologues of DMC (i.e., diethyl and dibenzyl carbonate), are excellent mono-C- and mono-N-alkylating agents, whereas asymmetrical methyl alkyl carbonates ($ROCO_2Me$ with $R \geq C_3$) undergo methylation processes with a chemoselectivity up to 99%.

Introduction

In the past decade, the public dialogue has increasingly addressed the environmental impact of the chemical substances, an issue fully recognized as a major concern. As a consequence, this awareness is pushing governments toward more severe laws for environment safeguards, which although beneficial, are becoming burdensome on industry budgets. To overcome the problem at the source, the chemical industry must develop cleaner chemical processes by the design of innovative and environmentally benign chemical reactions. *Green chemistry* offers the tools for this approach.[1]

Green organic syntheses must meet, if not all, at least some of the following requirements: avoid waste,[2] be atom-efficient,[3] avoid the use and production of toxic and dangerous chemicals, produce compounds that perform better as well as existing ones and are biodegradable, avoid auxiliary substances (e.g., solvents) or use eco-compatible solvents (water or dense CO_2), reduce energy requirements, use renewable materials, and use catalysts rather than stoichiometric reagents.[4]

To focus on the more specific area of the replacement of harmful and undesirable compounds, a relevant case is exemplified by methyl halides (CH_3X, X = I, Br, Cl), dimethyl sulfate (DMS), and phosgene ($COCl_2$), reagents used for methylation and carbonylation reactions, respectively. For instance, Scheme 1 shows the methylation of phenol by CH_3X and DMS to give anisole, and the alkoxycarbonylation of an alcohol by $COCl_2$. These toxic and waste-producing reagents have a valuable green alternative in dimethyl carbonate (DMC).

Since 1980, with the development of gas liquid-phase transfer catalysis (GL-PTC) as a new continuous-flow method for organic syntheses,[5] our group has had a long-standing interest in the use of DMC as an environmentally friendly substitute for DMS and CH_3X in methylation reactions and for phosgene in methoxycarbonylation reactions (Scheme 2).

Among the specific advantages of DMC, and of alkyl carbonates in general, is that their building block is CO_2, an environmentally benign compound, which does not cause emissions of volatile organic compounds (VOCs) in the atmosphere.

This Account reports on the reactivity of organic carbonates as alkylating agents, with emphasis on the lightest term of the series, DMC. Under both continuous-flow and batch conditions, DMC can react with a number of nucleophilic substrates, such as phenols, primary amines, sulfones, thiols, and methylene-active derivatives

Scheme 1. Methylation and Alkoxycarbonylation Using DMS, CH_3I, and $COCl_2$

$$PhOH + (CH_3)_2SO_4 + NaOH \longrightarrow PhOCH_3 + NaCH_3SO_4 + H_2O$$

$$PhOH + CH_3I + NaOH \longrightarrow PhOCH_3 + NaI + H_2O$$

$$2ROH + COCl_2 + 2NaOH \longrightarrow ROCOOR + 2NaCl + 2H_2O$$

Scheme 2. Methylation and Methoxycarbonylation Using DMC

$$PhOH + CH_3OCOOCH_3 \xrightarrow{\text{cat. base}} PhOCH_3 + CO_2 + CH_3OH$$

$$ROH + CH_3OCOOCH_3 \xrightarrow{\text{cat. base}} ROCOOCH_3 + CH_3OH$$

Scheme 3. Enichem Synthesis of DMC

$$2CH_3OH + 1/2O_2 + CO \xrightarrow{\text{Cu salts}} CH_3OCOOCH_3 + H_2O$$

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Maurizio Selva was born in 1962 and earned his doctoral degree (Laurea, cum laude) in industrial chemistry in 1989 at the University of Venice. In 1992, he was appointed researcher and joined the Department of Environmental Science at the University of Venice, where he is currently working. His research interests are in the field of organic synthesis, focused in the setting-up of both continuous-flow and batch methods for the performing of reactions with low environmental impact; in particular, with the use of (i) nontoxic dialkylcarbonates as selective mono-alkylating and alkoxycarbonylating agents, and (ii) dense CO_2 as a solvent/reagent. He is also involved in the study of new chemical methods for the degradation of halogenated aromatic pollutants. He is the author and co-author of ∼50 scientific papers.

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Table 1. Comparison between the Toxicological and Ecotoxicological Properties of DMC, Phosgene, and DMS

property	DMC	phosgene	DMS
oral acute toxicity (rats)	LD_{50} 13.8 g/kg		LD_{50} 440 mg/kg
acute toxicity per contact (cavy)	LD_{50} > 2.5 g/kg		
acute toxicity per inhalation (rats)	LC_{50} 140 mg/L; (4 h)	LC_{50} 16 mg/m^3; (75 min)	LC_{50} 1.5 mg/L (4 h)
mutagenic properties	none		mutagenic
irritating properties (rabbits, eyes, skin)	none	corrosive	
biodegradability (OECD 301 C)	> 90% (28 days)	rapid hydrolysis	rapid hydrolysis
acute toxicity (fish) (OECD 203)	NOEC[a] 1000 mg/L		LC_{50} 10−100 mg/L (96 h)
acute toxicity on aerobial bacteria of wastewaters (OECD 209)	EC_{50} > 1000 mg/L		

[a] NOEC = Concentration which does not produce any effect.

Table 2. Some Physical and Thermodynamic Properties of DMC

mp (°C)	4.6
bp (°C)	90.3
density (D^{20}_4)	1.07
viscosity (μ^{20}, cps)	0.625
flashing point (°C, O. C.)	21.7
dielectric constant (ϵ^{25})	3.087
dipole moment (μ, D)	0.91
ΔH vap (kcal/kg)	88.2
solubility H_2O (g/100 g)	13.9
azeotropical mixtures	with water, alcohols, hydrocarbons

of aryl and aroxy-acetic acids. The mechanistic and synthetic aspects of these processes will be detailed.

1. Properties of DMC

Many of the properties of DMC make it a genuinely green reagent, particularly if compared to conventional alkylating agents, such as methyl halides (CH_3X) and dimethyl sulfate (DMS) or to phosgene used as a methoxycarbonylating reagent (Scheme 1).

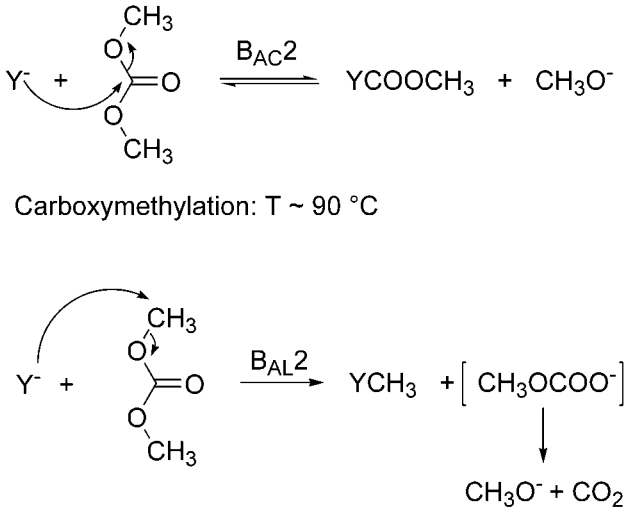
1. First of all, DMC is a nontoxic compound.[6] Since the middle 1980s, in fact, it has no longer been produced from phosgene, but rather by catalytic oxidative carbonylation of methanol with oxygen through a process developed by Enichem (Italy)[7] and UBE.[8] In addition to improving procedural safety, this method of producing DMC avoids contamination from phosgene and eliminates the need to dispose of byproduct inorganic salts. Some of the toxicological properties of DMC and phosgene and DMS are compared in Table 1.

2. DMC is classified as a flammable liquid, smells like methanol, and does not have irritating or mutagenic effects either by contact or inhalation.[9] Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS and the extremely toxic phosgene. Some physicochemical properties of DMC are listed in Table 2.

3. DMC exhibits a versatile and tunable chemical reactivity that depends on the experimental conditions. In the presence of a nucleophile (Y^-), DMC can react either as a methoxycarbonylating or as a methylating agent (Scheme 4).[10]

Although there is not always a clear cutoff between the two pathways of Scheme 4, it is generally observed that (i) at the reflux temperature (T = 90 °C), DMC acts primarily as a methoxycarbonylating agent by a $B_{AC}2$ (bimolecular, base-catalyzed, acyl cleavage, nucleophilic substitution) mechanism where the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification

Scheme 4. Nucleophilic Substitution on DMC by $B_{AC}2$ and $B_{AL}2$ Mechanisms



product. Under these conditions, DMC can replace phosgene. (ii) at higher temperatures (usually T = 160 °C), DMC acts primarily as a methylating agent: a $B_{AL}2$ (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution) mechanism predominates where the nucleophile attacks the methyl group of DMC.

Of the two, only the methylation reaction is irreversible, because the CH_3OCO_2H that is formed decomposes to methanol and CO_2.

Since both methylation and methoxycarbonylation generate CH_3O^-, both reactions can be conducted in the presence of catalytic amounts of base. This avoids the formation of unwanted inorganic salts as byproducts and the related disposal problems. In principle, the methanol produced can be recycled for the production of DMC.[11] In contrast, methylation with methyl halides or DMS, and carbonylation with phosgene generate stoichiometric amounts of inorganic salts.

2. Reaction Conditions

The development of a new eco-friendly process is often associated with advanced reaction technologies, an aspect that sometimes imposes a careful balance between the environmentally benign character and the economic/safety feasibility of the process itself. The use of supercritical CO_2 ($scCO_2$) is an example: $scCO_2$ is among the most attractive green alternatives to replace conventional solvents, although its handling requires high-pressure

operations (usually at $P > 130$ bar), which are energy-consuming and potentially dangerous.[12] This approach becomes a green solution only when real chemical benefits (higher selectivities, rates, yields) are achievable in the supercritical fluid.

Also in the case of DMC, reaction conditions are not apparently green: the methylating ability of DMC can be exploited at a temperature >160 °C (over the boiling point of DMC itself, 90 °C), which implies an autogenic pressure (>3 bar) for batchwise processes. Such conditions, however, are not prohibitive, especially in industrial practice where pressures up to 20−30 bar and temperatures up to 250 °C are not a concern.

Moreover, from the environmental standpoint, advantages must be seen on the global balance: the DMC-mediated alkylation reactions are much more safe than any other alkylation method known with conventional reagents. Not only the features of the reaction itself, but also the peculiarity of the reagent(s), the base (truly catalytic) and the absence of wastes are key aspects.

Discontinuous (batch) processes are carried out in pressure vessels (autoclaves) where DMC is maintained as a liquid by autogenous pressure. Instead, continuous-flow (c.-f.) reactions at atmospheric pressure require that both DMC and the reagent(s) in the vapor phase come into contact with a catalytic bed, a constraint that has spurred the development of new applications and alternative reaction engineering, namely, GL-PTC (gas−liquid-phase transfer catalysis) and continuously fed stirred tank reactor (CSTR).

Accordingly, under different conditions, DMC is used as a methylating reagent for a variety of substrates: phenols, thiols, thiophenols, aromatic amines, arylacetonitriles, arylacetoesters, aroxyacetonitriles, aroxyacetoesters, alkylaryl sulfones, benzylaryl sulfones, and lactones, either under continuous flow or in batch conditions.

2.1 Continuous Flow (c.-f.): Plug-Flow and CSTR Reactors. Under GL-PTC conditions, a gaseous stream of reagent and DMC flows over a catalytic bed usually composed of a porous inorganic material (usually corundum in the form of a spherical extrudate of 1−3 mm of diameter), which acts as a support for both an inorganic base (an alkaline carbonate) and a phase-transfer (PT) agent, such as phosphonium salts,[13] crown ethers,[14] and poly(ethylene glycol)s (PEGs). These latter, in particular, although less efficient than other PT agents, are desirable, because they are thermally stable, nontoxic, and inexpensive.[15]

In a typical configuration, the c.-f. methylation reaction with DMC takes place in a plug-flow reactor made by a bed of K_2CO_3 coated with PEG 6000 (0.5−5% mol equiv) and heated to 160−180 °C.[5,16] A mixture of DMC and substrate (YH) is fed into the reactor where the base generates the reactive nucleophilic anion (Y^-) from the substrate. The role of the PT agent is to complex the alkaline metal cation, thereby increasing the basic strength of the solid carbonate. As shown in the scheme of Figure 1, the immobilized PT agent is in the liquid phase throughout the reaction, and it allows the continuous transfer of the products and reactants between the gas and liquid phases. The methylated product is then condensed and collected at the other end.

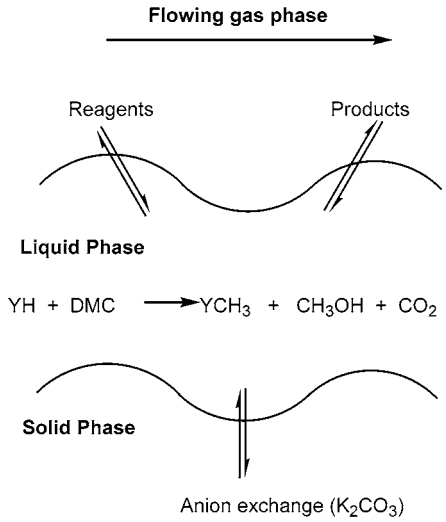
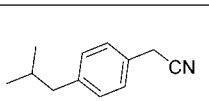
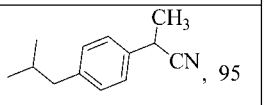


FIGURE 1. General mechanism of gas liquid-phase transfer catalysis (GL-PTC).

Table 3. Reactions of DMC with Different Nucleophiles under GL-PTC Conditions[a]

Entry	Reagent	Product (Yield, %)
1	ArOH	ArOMe, 100
2	ArSH	ArSMe, 100
3	ROH	$ROCO_2Me + (RO)_2CO$
4	$PhCH_2CN$	PhCH(Me)CN, 98
5		 95 Ibuprofen precursor

[a] Conditions: GL-PTC; plug-flow reactor; catalyst, K_2CO_3 coated with 0.5−5 mol % of PEG 6000; $T = 160-180$ °C.

Quantitative conversions are obtained from all the substrates listed in Table 3.[4,16,17] Moreover, in the case of CH_2-active compounds, the reaction proceeds with a monomethyl selectivity >99% (entries 4−5).

An example reaction is the methylation of phenol under GL-PTC conditions (Figure 2).

In a typical experimental procedure, when a mixture of phenol (94 g, 1 mol) and DMC (2.0 mol) is made to flow over a 100-g catalytic bed composed of 95 wt % K_2CO_3 g and 5 wt % PEG 6000 at 180 °C, pure anisole is recovered with a 100% yield in 1 h (residence time ∼ 10 s).[17a,b] Pyrocatecol and hydroquinone can also be selectively mono- or dialkylated under continuous flow conditions on a pilot plant scale.[10]

In Table 3, it should be noted, however, that hard alkoxide anions (RO^-) react with DMC via a $B_{Ac}2$ mechanism to yield exclusively transesterification products ($ROCO_2Me$) with no trace of methyl ethers (entry 3). Such a peculiar selectivity is presently under investigation.

An alternative c.-f. methodology for DMC methylations, was developed as well by using a continuously fed stirred tank reactor (CSTR, Figure 3).[18]

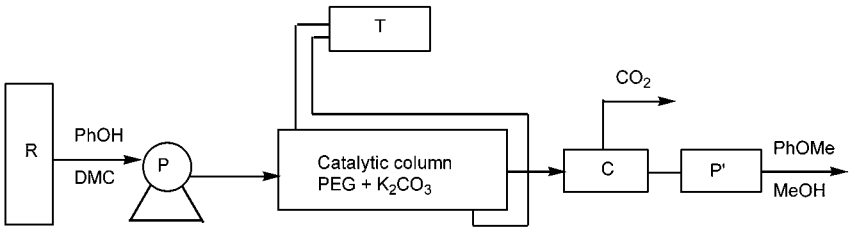


FIGURE 2. C.-f. methylation of phenol in a plug-flow reactor under GL-PTC conditions. R, reagent's reservoir; P, metering pump; T, thermostat; C, condenser; P′, product store.

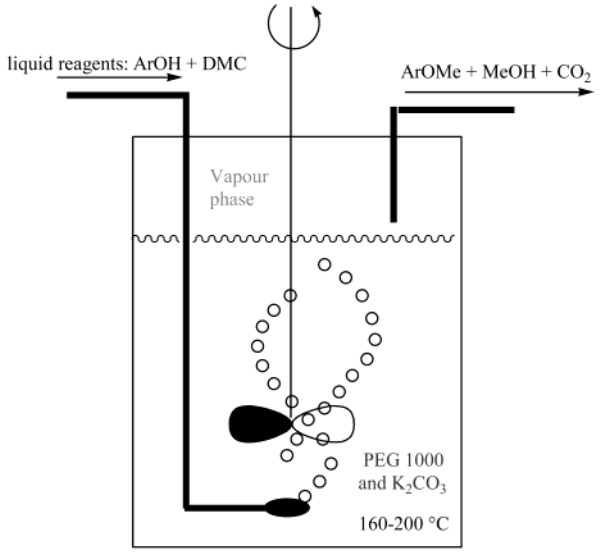
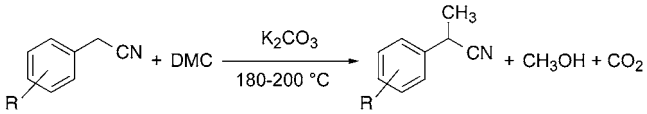


FIGURE 3. Schematic chart of a CSTR reactor for the O-methylation of phenols with DMC. Liquid reagents are vaporized by contact with the hot slurry (mechanically stirred), and bubbled through it. Reaction takes place instantaneously and anisoles are picked up from the vapor phase.

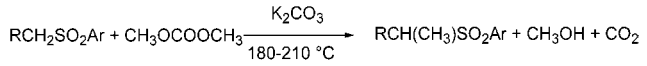
In this configuration, the catalyst fills the reactor in the form of a liquid slurry of the PT agent (usually PEG 1000) and K_2CO_3, and it is kept at the desired temperature (160−200 °C) under vigorous stirring. The mixture of DMC and the reagent is vaporized by coming into contact with the catalytic bed. When a suitable feeding rate is chosen, the apparatus works under gradientless conditions: the composition of the mixture collected at the outlet is equal to that present inside the reactor, and the reaction takes place instantaneously while reagents bubble through the bed. At atmospheric pressure, different phenols are transformed quantitatively into the corresponding anisoles with a WHSV (weight hourly space velocity) up to 9.5×10^{-2} h^{-1}.[10] The reaction could run without interruption for at least 2 weeks. Some results are listed in Table 4.

2.2 Batch Methylation Reactions with DMC. Under batch conditions, methylations with DMC must necessarily be run in sealed autoclaves, given its boiling point (90 °C) and the reaction temperature (>160 °C).

Scheme 5. Mono-C-methylation of Arylacetonitriles



Scheme 6. Mono-C-methylation of Alkylaryl Sulfones



Batch methylations with DMC can be performed on a number of different substrates, and under such conditions, the reaction mechanism can be conveniently investigated. In fact, the sampling of the reaction mixture at different conversions and the identification of possible intermediates (later in this Account) is easier with respect to c.-f. processes. For compounds susceptible to multiple methylation, the results are of special interest, since methylation with DMC totally inhibits multiple substitution in both *N*- and *C*-alkylation for primary aromatic amines and for CH_2-active compounds, respectively.

The most interesting and best-studied reaction, particularly in view of its selectivity, is the mono-C-methylation of arylacetonitriles (Scheme 5).

In the presence of a weak base (usually K_2CO_3), these compounds can be effectively mono-C-methylated with an unprecedented selectivity of >99% at complete conversions. For instance, when a mixture of $PhCH_2CN$, DMC, and K_2CO_3 in a 1:20:2 molar ratio, respectively, was allowed to react at 180 °C for 3.75 h, 2-phenylpropionitrile was obtained in a 95% yield with a purity >99%.[19] For comparison, in the same reaction run under PTC conditions and using CH_3I, the mono- to dimethyl derivative ratio never exceeded 2.4.[20] The very high monomethyl selectivity has turned out to be very interesting for the synthesis of precursors for antiinflammatory drugs. Some examples are listed in Table 5.

Similarly, in the presence of weak inorganic bases (K_2CO_3), the reactions of DMC with sulfones bearing α-methylenic groups (RCH_2SO_2R'; R = alkyl, Aryl; R′ = aryl) afford the respective mono-C-methylated compounds [$RCH(CH_3)SO_2R'$] with >99% selectivity at complete conversions (Scheme 6).[21]

Table 4. O-Methylation of Different Phenols (ArOH) with DMC in a CSTR[a]

ArOH, Ar	*T*, °C	flow rate, mL/h	flow time, h	substrate converted, g	product, ArOMe, %	WHSV × 100, g_{prod}/g_{bed} h
Ph	200	80	2.5	97.5	97	8.4
p-MeC_6H_4	160	80	4	128.0	98	9.5

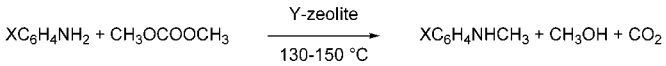
[a] Reactions carried out over a catalytic bed of PEG 1000 (300 g) and K_2CO_3 (6 g). Molar ratios: 1:1.05 for PhOH/DMC, and 1:1.5 for *p*-MeC_6H_4OH/DMC. WHSV: grams of ArOMe obtained hourly per gram of catalyst.

Table 5. Mono-C-methylation of Arylacetonitriles[a]

X	Ar	conversion %	selectivity in mono-C-methylation	intermediate for
CN	4-isobutylphenyl	99	99	Ibuprofen
CN	3- carboxymethylphenyl	100	> 99	Ketoprofen
$COOCH_3$	2-(6-methoxynaphthyl)	100	> 99	Naproxen

[a] Conditions: autoclave; substrate/DMC/K_2CO_3 = 1:18:2 molar ratio; T = 180−220 °C.

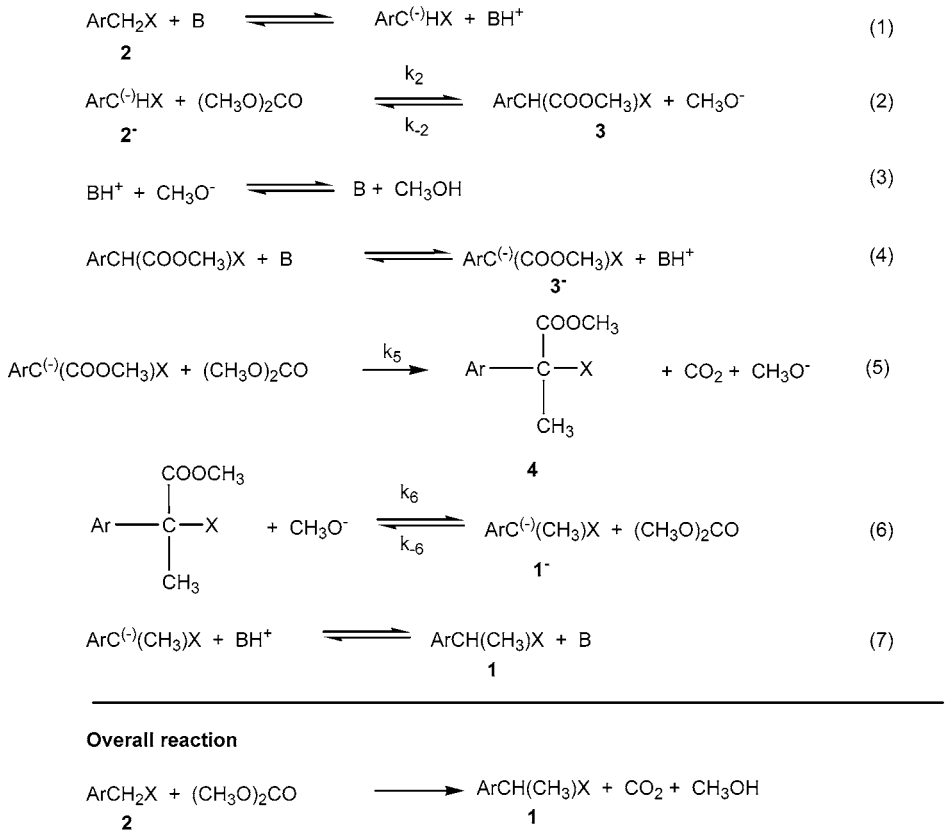
Scheme 7. Mono-N-methylation of Aromatic Amines



$XC_6H_4NH_2$, X	Catalyst	T/°C	t/min	Cat. : Substrate [a]	ArNHMe (Yield, %)	Selectivity, % (Mono/di) [b]
H	NaY	130	195	1.2	84	98
	K_2CO_3	180	220	1.8	13	87 [c]
	-	150	200	-	2	100
p-NO_2	KY	150	600	3.3	79	93
p-CN	KY	150	270	3.3	83	98
o-CO_2Me	NaY	150	330	3.3	84	96
2,6(Me)$_2$	NaY	150	300	3.3	76	94

[a] Weight quotient between the catalyst and the amine. [b]The percent selectivity is calculated using the expression {[ArNHMe] + [ArNMe$_2$])} × 100. [c]34% of PhN(Me)CO_2Me was a byproduct.

Scheme 8. Mechanism of the Mono-C-methylation of CH_2-Active Compounds (X = CN, CO_2CH_3) with DMC



It is noteworthy that in the case of methyl sulfones ($ArSO_2Me$), the reaction proceeds with the homologation of the methyl to an *i*-propyl group; that is, the methylation is still highly selective toward the substitution of only two of the methyl protons. Aside from the synthetic results, this observation is relevant from the mechanistic viewpoint, as will be clarified in the discussion of Scheme 8.

Under the same conditions (batch or GL-PTC) discussed for CH_2-acidic compounds, primary aromatic amines also react with DMC. In this case, although the reaction selectively yields the mono-N-methylated amines with no dimethylated byproducts, sizable amounts of methyl carbamates ($ArNHCO_2Me$) are formed.[10,17c] Much better results can be gathered in the presence of zeolites, particularly alkali metal-exchanged Y and X faujasites.

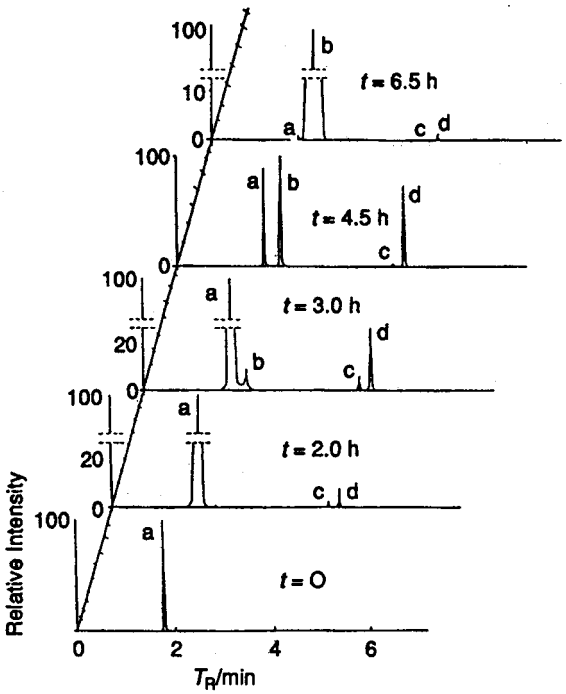


FIGURE 4. The mono-C-methylation of *o*-tolylacetonitrile with DMC. Gas chromatograms refer to different reaction times: (a) *o*-$CH_3C_6H_4CH_2CN$, (b) *o*-$CH_3C_6H_4CH(CH_3)CN$, (c) *o*-$CH_3C_6H_4CH(CO_2Me)CN$, and (d) *o*-$CH_3C_6H_4C(Me)(CO_2Me)CN$.

These aluminosilicates possess pseudospherical cavities (supercavities) of 11. 8 Å in diameter that can be accessed through channels whose size is 7.4 Å.[22]

In the presence of these solid catalysts, different anilines, even deactivated by both electronic and steric effects, yield the corresponding mono-N-methyl derivatives [ArNHMe] with selectivities of 93−98% at conversions up to 95% (Scheme 7). [23]

In summary, all the nucleophiles indicated up to now are efficiently methylated (and monomethylated where applicable) with DMC, under both c.-f. and batch conditions.

3. Monomethyl Selectivity: The Reaction Mechanism

CH_2-Acidic Compounds. The methylation of arylacetic acid derivatives is chosen as a model reaction for the mechanistic discussion. Experimental evidence of DMC-mediated alkylation of $ArCH_2X$ (X = CN, CO_2Me) with DMC supports the hypothesis that the reaction does not proceed through a S_N2 displacement of the $ArCH^{(-)}X$ nucleophile on DMC ($B_{Al}2$ mechanism).[19a] Rather, the selectivity arises from consecutive reactions involving two intermediate species observed during the reaction: $ArCH(CO_2Me)X$ (**3**) and $ArC(CH_3)(CO_2Me)X$ (**4**).

As an example, Figure 4 depicts the outcome of the mono-C-methylation of *o*-tolylaceto nitrile with DMC: the two compounds *o*-$CH_3C_6H_4CH(CO_2Me)CN$ and *o*-$CH_3C_6H_4C(Me)(CO_2Me)CN$ (shown as **c** and **d**) are the reaction intermediates.

In general, however, intermediates **3** are very reactive moieties (as confirmed by the kinetic investigation of the reaction; see later in this Account) whose identification in the reaction mixture fails very often. In the case of Figure 4, it is probably the presence of an *o*-Me substituent that affects both the stability and reactivity of compound **c**.

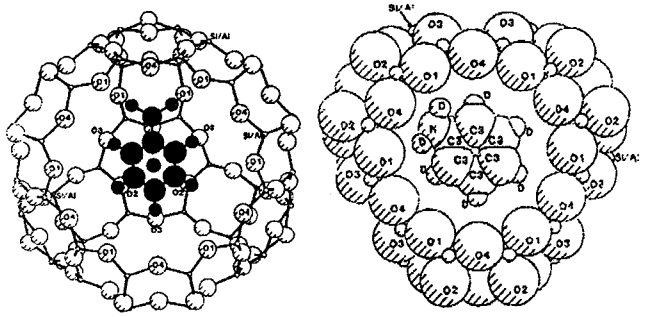


FIGURE 5. Two adsorption sites for $PhND_2$ in the NaY faujasite.

The pattern for the reaction mechanism is outlined in Scheme 8.

Initially, the carbanion $[ArCH^{(-)}X]$ undergoes a methoxycarbonylation reaction by an attack on the acyl carbon of DMC ($B_{Ac}2$ mechanism). The resulting intermediate $[ArCH(CO_2Me)X$, (**3**)] reacts through its anion $[ArC^{(-)}(CO_2Me)X$, (**3**$^-$)] with the alkyl carbon of DMC to yield the corresponding methyl derivative $[ArC(CH_3)(CO_2Me)X$, (**4**); $B_{Al}2$ mechanism]. Finally, compound **4** is subjected to a demethoxycarbonylation reaction to the final product $[ArCH(CH_3)X]$.

This mechanism also applies to other CH_2-active compounds, such as derivatives of aroxyacetic acid and benzylic sulfones, whose methylation reactions with DMC proceed through the corresponding methoxycarbonylated and methyl methoxy carbonylated intermediates [$WCH(CO_2Me)X$ and $WC(Me)(CO_2Me)X$; W = ArO, X = CN, CO_2Me; W = Ar, X = SO_2R].

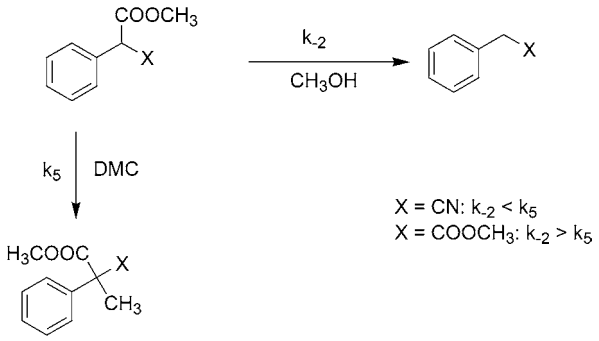
In the particular case of methyl sulfones ($ArSO_2Me$), the pathway of Scheme 8 also accounts for the above-mentioned homologation of the methyl-to-*i*-propyl group. In fact, once the methoxycarbonylated compound $ArSO_2CH_2CO_2Me$ is formed, only two protons remain available for the further methylation step.

To investigate in more depth the mechanism of Scheme 8, a detailed kinetic analysis has been performed by choosing the methylation of phenylacetonitrile (**2a**) and methyl phenylacetate (**2b**) with DMC as model reactions.[24] Some general considerations are the following.

In the case of compound **2a**, the rate-determining step of the overall transformation is the methoxycarbonylation reaction (step 2). The similarity of k_{-2} and k_6 reveals that both the starting reagent **2a** and its methyl derivative **1a** undergo demethoxycarbonylation reactions at comparable rates, whereas the methylation step of the intermediate **4a** is the fastest reaction. In particular, at 140 °C, the pseudo-first-order rate constants of steps 6, 5, and the reverse of 2, namely k_6, k_5, and k_{-2}, of Scheme 8 are 2.9×10^{-3}, 7.9×10^{-3}, and 2.7×10^{-3} min^{-1}.[25]

Overall, the comparison of the kinetic behavior of the investigated steps reveals that the nonequilibrium me-

Scheme 9. Demethoxycarbonylation (k_2) vs Methylation (k_5) for CH_2-Active Compounds



thylation reaction is crucial in driving the overall process to completion. In fact, the higher rate of step 5 allows both the rapid consumption of **3a** and the accumulation of **4a,** which serves as a reactant for step 6. In other words, both equilibria 2 and 6 are controlled by irreversible reaction 5.

The mechanism shows the key action of the methoxycarbonyl group that, by increasing the acidity of **3,** acts as a promoter, significantly accelerating step 5.

At a high temperature, it is known that the lack of solvation may favor a $B_{Al}2$ mechanism with respect a $B_{Ac}2$ one.[26] In the case of DMC-mediated methylations, both reaction pathways occur in a definite sequence, which accounts for the high monomethyl selectivity observed in these reactions. The reasons for the promoting effect of the $-CO_2Me$ group as well as the progression of $B_{Ac}2/B_{Al}2$ mechanisms are still not completely understood.

Finally, it should be noted that esters and nitriles in the demethoxycarbonylating step behave in a manner opposite to that in the methylating step. For nitriles, the methylation rate predominates over methoxycarbonylation; for esters, demethoxycarbonylation predominates (Scheme 9).

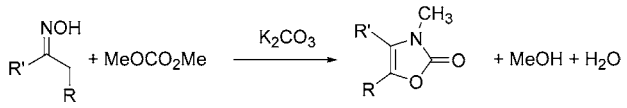
Amines. As for the mono-N-methyl selectivity observed in the reaction of primary amines with DMC, the experimental investigation supports a mechanism similar to that reported in Scheme 8, though in this case, the zeolite cages assist the reactions.[21]

In particular, it is assumed that the amine is adsorbed in the zeolite pores: as an example, Figure 5 reports the adsorption sites described for the case of deuterated aniline.[27]

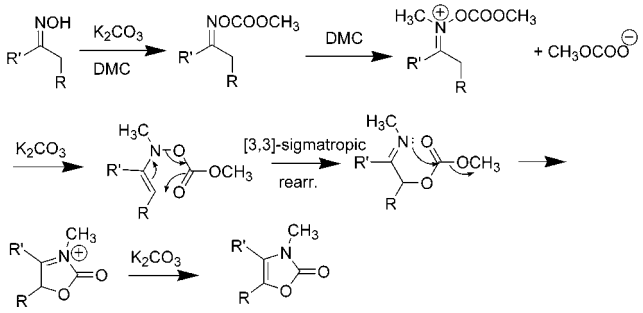
Two different sites are indicated: the first (Figure 5a) is in the proximity of a cation Na^+ which forms a π complex with $PhND_2$. The ion is the black dot perfectly centered in the aromatic ring of the aniline. In the second (Figure 5b), the amine is held by the interactions with the 12 oxygen atoms that form the supercavity of the zeolite.

During the reaction, the oxygen atoms of the zeolite framework act as basic sites and promote the formation of a methyl carbamate ($ArNHCO_2Me$). Because of its high polarity, this compound is retained in the cage, where it undergoes *N*-methylation to $ArN(Me)CO_2Me$ and, finally, demethoxycarbonylation to the desired product (ArNHMe). In particular, the demethoxycarbonylation is favored by the presence of weakly acidic sites, such as the metal cations of the zeolites. On the whole, the selectivity in *N*-methylation reactions comes from a synergistic effect of the dual reactivity of DMC and the acid−base properties of the zeolites along with the steric constraints of their cavities.

Scheme 10. *N*-Methyl Oxazolinones from Oximes



Scheme 11. Mechanism for the Synthesis of *N*-Methyl Oxazolinones from Oximes



4. DMC as a Methoxycarbonylating Agent

As shown in Scheme 4, selective methoxycarbonylation reactions with DMC are usually performed at relatively low temperatures. However, we have reported some interesting examples of this reactivity at higher temperatures and dependent on the nucleophilicity of the substrates. These will be discussed in the following section.

4.1 Oximes. At 180−190 °C and in the presence of a weak base (usually K_2CO_3), ketoximes bearing an α-methylene react with DMC to yield *N*-methyl oxazolinones (Scheme 10).[28]

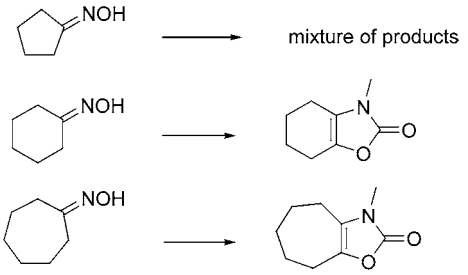
This reaction is general for both linear and cyclic oximes, and it exemplifies a selective methoxycarbonylation reaction at a high temperature. In fact, the first step is the $B_{Ac}2$ attack of the oxygen atom on the DMC carbonyl. Then the reaction proceeds through a *N*-methylation and a final [3,3]-sigmatropic rearrangement,- as shown in Scheme 11.

Although oximes are ambident nucleophiles, a neat regioselectivity allows the formation of oxazolinones. The α effect, which is especially relevant for the substitution of $R_2C{=}NO^-$ anions at a carbonyl carbon,[29] may offer a good explanation for the $B_{Ac}2/B_{Al}2$ sequence (*O*-methoxycarbonylation and *N*-methylation reactions, respectively) in Scheme 11.

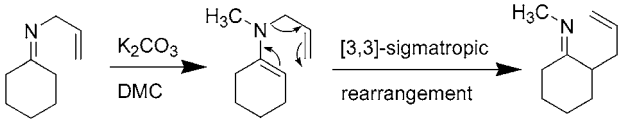
This reaction is also the first ever reported example of a sigmatropic rearrangement involving DMC. Further evidence for this mechanism has been gathered by us from the comparison of the reactivity of C_5-C_7 cyclic oximes that is resumed in Scheme 12.

As can be seen, cyclohexanone- and cycloheptanone oximes give the cyclic rearranged products, whereas

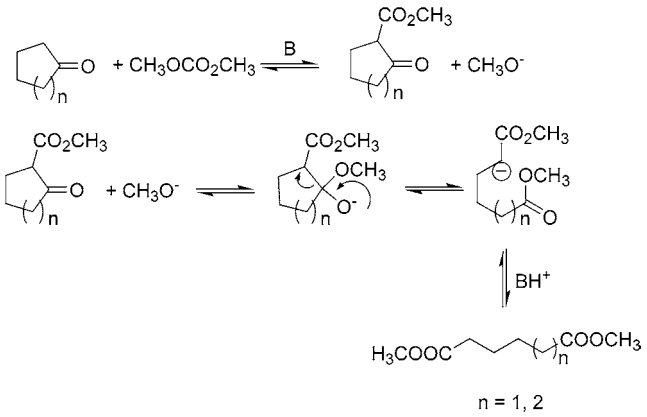
Scheme 12. Reactivity of C_5-C_7 Cyclic Oximes



Scheme 13. Reaction of *N*-Cyclohexylideneallylimine with DMC



Scheme 14. α,ω-Diesters from Cyclic Aliphatic Ketones



cyclopentanone oxime yields a complex reaction mixture with not even a trace of the corresponding oxazolinone. Since sigmatropic rearrangements proceed through a highly ordered transition state,[30] the required geometry is perhaps not achieved when a more strained C═C bond is involved, as occurs in the rigid cyclopentene ring.

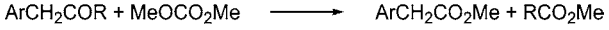
In addition, the reaction of allylimines with DMC give rearranged products. As an example, *N*-cyclohexylideneallylimine undergoes *N*-methylation by DMC followed by an aza-Claisen rearrangement (Scheme 13).[28]

4.2 Ketones. At a high temperature (>200 °C), a very attractive application of DMC as a methoxycarbonylating agent is the reaction with alicyclic ketones. In particular, cyclopentanone and cyclohexanone when reacted with DMC (or DEC) and a base (K_2CO_3) yield adipic and pimelic dimethyl (or diethyl) esters, respectively (Scheme 14).[31]

In fact, these diesters are of major industrial interest as building blocks for nylon 6,6 and nylon 7,7 in the production of polyesters and polyamides.[32] However, their present synthesis raises an environmental concern. For instance, the oxidation of cyclohexanone by nitric acid (for the preparation of adipic acid) accounts for >10% of the total yearly release of N_2O, which is among the main gases responsible for the greenhouse effect.

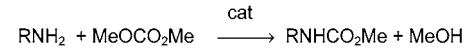
The reaction of Scheme 14 represents an eco-friendly alternative synthesis of α,ω-diesters which uses green reagents and, relevantly, has a 100% atom economy.[3] The

Scheme 15. Reaction of Benzylic Ketones with DMC



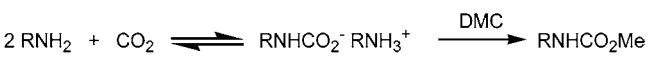
Ar and R = Ph and *p*-tolyl.

Scheme 16. Carbamation of Amines with DMC



Cat.: strong bases, Pb(II), alumina.

Scheme 17. Carbamation of Amines with DMC in the Presence of CO_2



overall process is mechanistically described as a retro-Claisen condensation.

The reaction is even more general and applicable to ketones bearing an α-methylene. Yields up to 90% of the corresponding dimethyl esters are obtained in the case of benzylic substrates (Scheme 15).

4.3 Amines. The carbamation of primary amines with DMC is a known process, though only catalyzed reactions proceed with good yields and selectivity (Scheme 16).[33]

Our group very recently reported that the reaction of Scheme 17 when operating at 130−140 °C can proceed efficiently (yields up to 83% in methyl carbamates) without any catalyst in the presence of supercritical carbon dioxide ($scCO_2$) and at 90 bar.[34] $scCO_2$ plays a double role in this reaction: (i) it acts as a catalyst in the formation of the active nucleophiles (Scheme 17) and (ii) at a pressure over 90 bar, it inhibits the formation of *N*-methylated carbamates [$RN(Me)CO_2Me$], which are possible byproducts.

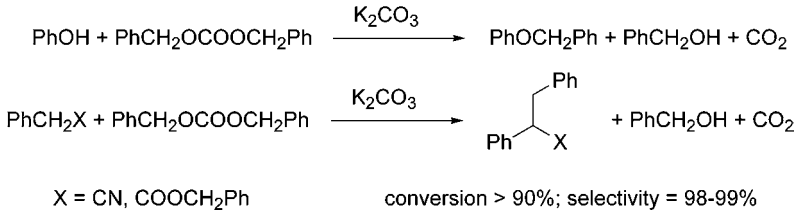
5. Other Organic Carbonates

Higher homologues of dialkyl carbonates exhibit alkylating/carboxyalkylating reactivity and selectivity similar to that of DMC. The main difference concerns the reaction rates, which as the alkyl chain of the carbonate increases, undergo a neat decrease according to the steric expectations for nucleophilic displacements. An exception, of course, is dibenzyl carbonate, owing to the resonance stabilizing effect of the benzyl group in the S_N2 transition state. In line with this observation, benzylation, and more specifically, mono-C- and mono-N-benzylation reactions, take place at rates comparable to that of the corresponding methylation processes (see Table 5).

5.1 Dibenzyl Carbonate (DBnC). Because of the higher boiling point, DBnC allows much simpler conditions with respect to DMC: reactions can be performed at atmospheric pressure in normal glass apparatus. This fact, along with the peculiar high selectivity observed (at almost complete conversion) facilitates workup and separation of the mono-C-alkyl product. DBnC can be used to benzylate phenylacetonitrile, benzyl phenylacetate, and phenol, in refluxing DMF with a K_2CO_3 catalyst (Scheme 18).[35] The mechanism is analogous to the one sketched out for DMC (Scheme 8) and involves consecutive carboxybenzylation/benzylation steps.

5.2 Mixed Organic Carbonates. Asymmetrical alkyl methyl carbonates of the general formula $ROCO_2CH_3$,[36]

Scheme 18. Benzylation of Phenol and CH_2-Active Compounds with DBzlC



Scheme 19. Methylation of Phenols with Mixed Organic Carbonates ($ROCO_2CH_3$)

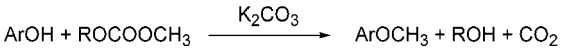


Table 6. Reactions of Phenol with Different Alkyl Methyl Carbonates[a]

			products (%)	
entry	R	time (h)[b]	$PhOCH_3$	PhOR
1	Et	15	90	10
2	*n*-Pr	17	95	5
3	*n*-Bu	15	97	3
4	$CH_3O(CH_2)_2O(CH_2)_2$	20	>99	
5	Bn	5	84	16
6	allyl	21	83	17

[a] T = 120 °C, phenol (3.3 mmol)/K_2CO_3,/**3** = 1:1.1:5. DMF (30 mL). [b] Time for complete conversion of the substrate.

Table 7. O-Methylation of Different Phenols by Methyl 2-(2-Methoxyethoxy)ethyl Carbonate[a]

entry	Ar	conversion (%)	yield (%) [b]	purity (%)
1	Ph	100	81	>99
2	*p*-MePh	100	79	>99
3	2-naphthyl	100	83	>99

[a] T =140 °C, substrate/K_2CO_3/MEC = 1:1.1:5 triglyme (50 mL). [b] Isolated yields of O-methylated derivatives.

can be conceived as selective methylating agents, since their reactivity is discriminated by the structure and the length of the alkyl chain R. In addition, it is the R group that imparts a practical advantage to the synthetic procedure: if heavy enough, it raises the boiling point of the carbonate so that methylation reactions are allowed at ambient pressure. This overcomes one of the major operative drawbacks of batch methylations with DMC, that is, the need for pressure vessels. This idea was recently developed by our group in the investigation of the O-methylation of phenols (Scheme 19).[37]

Some results are reported in Table 6. As can be seen, asymmetrical carbonates afford highly chemoselective methylation reactions, providing that R has at least three carbon atoms (R ≥ *n*-C_3, entries 2−4). Yet, in the case of reactive benzyl or allyl termini, the O-alkylation (forming PhOR) competes significantly with the formation of anisole (entries 5−6).

Most satisfactory results can be obtained with the use of 2-(2-methoxyethoxy)ethyl carbonate [$CH_3O(CH_2)_2O$-$(CH_2)_2OCOOCH_3$, **MEC**, entry 4] which allows O-methyl selectivity up to 99% for different phenols (Table 7).

More recently, the use of MEC has been reported by us also in the methylation of primary aromatic amines (*p*-$XC_6H_4NH_2$, X = H, Cl, NO_2).[38] In the presence of a NaY faujasite and at atmospheric pressure, the reaction proceeds with a complete methyl chemoselectivity and, most importantly, with a mono-N-methyl selectivity (90−97%) comparable to that achievable with DMC. As for DMC, selectivity arises from a synergistic effect of the reactivity of the carbonate and the amphoteric properties of the zeolite. In this case, however, a preliminary kinetic investigation has been performed using alkyl- and alkoxy-substituted anilines, and it allows some general conclusions.[39] This analysis indicates that the reaction selectivity toward methylated anilines (ArNHMe) does not depend on the polarity of the reaction solvent (when used), whereas a key role is played by the size of the zeolite cavities. In fact, as the bulkiness of the substituents grows, selectivity drops as well, because the diffusion of bigger molecules into the cavities is more and more difficult to a point that it becomes forbidden. For instance, from aniline to *p*-butylaniline, selectivity decreases from 99 to 90%, accompanied by a decreased conversion from 100 to 9% (at comparable reaction times). Even more impressive is the drop with 3,5-di-*tert*-butylaniline whose size cannot fit the zeolite pores and yields a 82% selectivity with 9% conversion.

These results represent the first ever reported evidence of a strict cooperation between the steric requisites of the faujasite catalyst and the peculiar reactivity of an asymmetrical carbonate in inducing simultaneously high methyl chemoselectivity and mono-N-methylselectivity for primary amines.

Concluding Remarks: The Green Context and Future Directions

In 1912, Giacomo Ciamician, the founder of organic photochemistry, wrote: "On arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry but mankind is."[40]

These concepts that a century ago were the property of fervid imagination and fantasy of enlightened scientists but blurred to most of the people are in the present days fully recognized and consciously encoded by green chemistry. In fact, this sentence has a striking match with the principles of green chemistry.[1] Particularly, it foreshadows the rejection of polluting industry; the use of renewable

sources of energy, such as solar energy; and the need for organic processes to mimic natural transformations.

In this context, DMC and other dialkyl carbonates offer powerful perspectives for the development of alkylation/carboxyalkylation methods having a low environmental impact. Moreover, these reactions are catalytic processes whose high selectivity allows minimization of the production of both waste and unwanted byproducts.

Much more than in any previous period, mankind is living the binomial of "safeguarding the environment" and "implementation of the quality of life" where chemistry is the key science and, particularly, investigations in the green chemistry area have to be a growing commitment for the chemical community.

Educational programs in green chemistry that are blossoming within IUPAC and other scientific organizations are establishing a new basis for the communication between chemical sciences and society.

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